

Amlodipine Better Than Lisinopril? How One Randomized Clinical Trial Ended Fallacies From Observational Studies

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The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) compared in >30 000 high-risk hypertensive patients the effects on coronary heart disease of 3 treatment strategies: (1) based on the diuretic chlorthalidone, (2) the calcium-channel blocker (CCB) amlodipine, and (3) the angiotensin converting-enzyme (ACE) inhibitor lisinopril, respectively.¹ Sponsored by the National Heart, Lung, and Blood Institute, ALLHAT stands out because no differences occurred in the incidence of the primary end point that consisted of the combination of fatal coronary heart disease and acute myocardial infarction.¹ Not surprisingly, the attention of the ALLHAT consortium shifted to secondary end points, such as stroke, or to loosely defined² components of secondary end points, such as heart failure. At the end of the line, the ALLHAT investigators based their main conclusions on events that, at the initiation of the trial, they regarded as “soft data that will at best confirm or supplement the primary endpoint.”³ More importantly, what was not identical in the 3 treatment groups was the on-treatment blood pressure despite vigorous attempts to titrate and combine the study medications to achieve a blood pressure of <140 mm Hg systolic and 90 mm Hg diastolic.¹ These salient features of ALLHAT should be kept in mind whenever one attempts to interpret the findings of this landmark trial.

In this issue of *Hypertension*, Leenen et al⁴ published a post hoc analysis, in which they made a direct comparison of cardiovascular and other outcomes among the 18 102 ALLHAT participants randomly assigned to amlodipine or lisinopril. In line with previous reports,¹ the incidence of the primary coronary end point and total and cardiovascular mortality were similar in both groups. However, the patients randomly assigned to lisinopril experienced higher risks of stroke, combined cardiovascular disease, gastrointestinal bleeding, and angioedema, whereas the risk of heart failure was higher in the amlodipine group.⁴ The excess cardiovascular risk was particularly apparent in women and black patients. Leenen et al⁴ concluded that

“considering the totality of outcome measures in ALLHAT, amlodipine appeared to have advantages over lisinopril.” This is a provocative statement that is in line with the published literature (Table) and that is prone to at least dent, if not shatter, the halo surrounding the ACE inhibitors. The conclusions of Leenen et al⁴ underscore the difficulty in bridging the gap between scientifically attractive pathogenetic concepts based on experimental models⁵ and the clinical reality that matters to patients, that is, event-free survival.

The ALLHAT investigators attributed at least part of the better cardiovascular outcome on amlodipine compared with lisinopril to the more pronounced blood pressure reduction on the CCB, particularly in women and black patients.⁴ The Heart Outcomes Prevention Evaluation study (HOPE)⁶ and the Losartan Intervention For Endpoint reduction in hypertension study (LIFE)⁷ launched the notion of benefit beyond blood pressure lowering, although in both trials the baseline-adjusted systolic blood pressure at the last visit was significantly lower in the patients randomly assigned to the ACE inhibitor (3.0 mm Hg; $P<0.001$)⁶ or the angiotensin II receptor blocker (1.3 mm Hg; $P=0.017$)⁷ than in those allocated placebo⁶ or atenolol,⁷ respectively. Stroke is the complication of hypertension that is most directly linked to the blood pressure level.⁸ Not surprisingly, metaregression analyses published by us^{9,10} and other researchers¹¹ demonstrated that, in keeping with large-scale prospective observational studies¹² and also in randomized clinical trials, small gradients in the achieved systolic blood pressure explain most of the differences in the cardiovascular outcomes. An updated metaregression analysis¹³ accounted not only for the differences in the achieved systolic blood pressure between groups randomly assigned in clinical trials but also for drug class, the interaction between on-treatment systolic pressure and drug class, age at randomization, year of publication, and duration of follow-up. The updated results corroborated that blood pressure reduction was by far the most important determinant of cardiovascular outcome.¹³ In keeping with the current ALLHAT findings, CCBs compared with ACE inhibitors provided a small blood pressure-independent benefit ($\approx 14\%$; $P=0.042$) in the prevention of stroke, and the same was true for ACE inhibitors compared with CCBs in relation to coronary heart disease ($\approx 10\%$; $P=0.028$).¹³ The observation that the incidence of the primary end point was similar in the 2 treatment groups in the study of Leenen et al⁴ might be interpreted as indirect evidence suggesting that lisinopril-based therapy conferred greater cardiac benefit than treatment initiated with amlodipine.

In 2003, the Blood Pressure Lowering Trialists' Collaboration noticed that for every outcome other than heart failure, the differences between randomized groups in cardiovascular

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Amlodipine Versus Other Reference Treatment in the Prevention of Myocardial Infarction or Stroke

Comparator	Trial	N	Coronary Heart Disease		Stroke	
			OR (95% CI)	P	OR (95% CI)	P
Versus placebo	PREVENT	825				
	CAMELOT	1318	0.69 (0.49 to 0.97)	0.031	0.60 (0.36 to 0.98)	0.038
	IDNT	1136				
Versus diuretics/ β -blockers	ALLHAT	24309				
	ASCOT	19257	0.96 (0.89 to 1.03)	0.26	0.86 (0.78 to 0.95)	0.002
Versus ACE inhibitors	ALLHAT	18102				
	CAMELOT	1336	1.01 (0.91 to 1.12)	0.89	0.82 (0.71 to 0.94)	0.004
Versus angiotensin II receptor blockers	IDNT	1146				
	VALUE	15245	0.82 (0.71 to 0.96)	0.009	0.84 (0.72 to 0.99)	0.032

N indicates the number of patients included from each trial; OR, odds ratio. Pooled ORs with 95% CIs were computed from the number of events (amlodipine/reference) and the number of patients per group randomly assigned in each trial by use of stratified 2 \times 2 contingency tables. Coronary heart disease included coronary mortality and acute myocardial infarction in ALLHAT and ASCOT; fatal and nonfatal myocardial infarction in CAMELOT, IDNT, PREVENT, and VALUE; and nonfatal myocardial infarction in CAMELOT. The trial acronyms are given in Reference.¹⁰

outcomes were directly related to the achieved systolic blood pressure.¹¹ However, the lack of association among 34 reviewed trials was mainly because of the noise of 4 that compared CCBs to placebo. The summary statistic breaking the relationship included results from a primary prevention trial in older patients and from 3 secondary prevention studies in diabetic patients with renal dysfunction or in high-risk patients with coronary heart disease.¹¹ Substantial differences in the pathogenetic mechanisms causing left ventricular failure in such heterogeneous conditions cast doubt on the proposed conclusion of no association between the prevention of heart failure and the level of achieved systolic blood pressure.¹¹ In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA)¹⁴ and in A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION),¹⁵ the relative risks of heart failure were slightly (hazard ratio: 0.84; 95% CI: 0.66 to 1.05; $P=0.13$)¹⁴ or significantly (hazard ratio: 0.71; 95% CI: 0.54 to 0.94; $P=0.015$)¹⁵ lower for the CCB compared with atenolol¹⁴ or placebo¹⁵ and followed the gradients in systolic blood pressure, amounting to 2.7 mm Hg¹⁴ and 6.0 mm Hg,¹⁵ respectively. In line with the epidemiological evidence linking heart failure to hypertension, these observations^{14,15} suggest that blood pressure lowering by a CCB or any other class of antihypertensive agents contributes to the prevention of left ventricular dysfunction.

Remarkably, in ALLHAT,^{1,4} as well as in the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE),¹⁶ heart failure, against the blood pressure gradient, occurred more frequently on amlodipine than on lisinopril^{1,4} or valsartan.¹⁶ This could either indicate that, for a given fall in blood pressure, blockers of the renin–angiotensin system are more powerful in preventing heart failure than are CCBs or that blood pressure is a less important predictor of congestive heart failure than of heart attack and stroke. However, in both trials,^{1,4,16} the Kaplan–Meier estimates for heart failure only started to diverge after 2 to 3 years, when, compared with the amlodipine arm, a greater proportion of patients randomly assigned to the ACE inhibitor^{1,4} or the angiotensin II receptor blocker¹⁶ had stopped the alterna-

tive first-line treatment, had crossed over, and/or were receiving combination therapy, including second-line antihypertensive medications.

Most clinicians regard ACE inhibitors as being well-tolerated antihypertensive drugs. Unexpectedly, in the current ALLHAT report, adherence to randomized treatment was significantly lower in the lisinopril than in the amlodipine arm (at 5 years, 72.6% versus 80.4%). Persistence was lowest in women and blacks. The reason for this difference is unclear but is likely to be because of adverse effects, frequently dry cough on ACE inhibitors and ankle edema on CCBs. For drugs that are used by hypertensive patients over decades, long-term safety is of paramount concern. Angioedema is a well-documented but rare adverse event in patients taking ACE inhibitors. It can appear from a few hours to 8 years after an ACE inhibitor is first taken. Unfortunately, a median of 10 months may elapse before onset of angioedema and withdrawal of the ACE inhibitor.¹⁷ This potentially fatal adverse event was observed in 38 patients in the lisinopril group but only in 3 randomly assigned to amlodipine. In the lisinopril arm, the rates were 0.72% in blacks and 0.26% in nonblacks. Although fatalities of angioedema are exceedingly rare, one should consider that as worldwide 30 to 40 million patients are exposed to ACE inhibitors, this drug class might account for several hundred fatalities per year.¹⁸ That these are not just hypothetical numbers is underscored by instances of fatal angioedema in both ALLHAT^{1,4} and HOPE⁶ and also by a recent report from a single coroner's office describing 7 cases of asphyxiation associated with ACE inhibitors within a mere 3-year period of time.¹⁹

Finally, how should clinicians translate the new ALLHAT findings in their day-to-day practice? Foremost, they should be aware that high blood pressure is a reversible risk factor with lower levels leading to fewer strokes and heart attacks. Furthermore, several landmark trials, over and above those listed in the Table (for review, see Reference 10), proved in no uncertain terms that CCBs are powerful, efficacious, and safe antihypertensive drugs and that they can be prescribed to high-risk patients as first-line drugs for indications that were until now dominated by inhibitors of the renin–angiotensin

system. Finally, observational studies, which are prone to observer bias, should never be taken at face value, even if they make headlines in the medical and lay media and even if, in some instances, they might be hypothesis generating. The analysis of Leenen et al⁴ puts a definite end to what was called the CCB controversy, which flourished for more than a decade. Only randomized trials provide evidence strong enough to be useful in the management of hypertensive patients, which currently already represent 20% to 30% of the world's population, a proportion likely to steadily increase over the next decades.

Disclosures

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